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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,879	09/30/2005	Lyubov Ryabova	58763.000029	5249

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,879	RYABOVA ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 9-14 and 23-24 have been canceled. Claims 1-8 and 15-22 are still at issue and are present for examination. Applicants' arguments filed on 1/19/08, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The rejection of claims 1-8 and 15-22 under 35 U.S.C. 103(a) as being unpatentable over Blakesley et al. (WO 98/22615) in view of Swartz et al. (WO 00/55353) is withdrawn as applicants have convincingly argued that one of ordinary skill in the art would not have found it obvious to use the method of Blakesley et al. in an *in vitro* transcription and translation system such as that of Swartz et al. Applicants argue that one of ordinary skill in the art would have understood that pyrophosphorolysis is not a problem in transcription reactions as it is in DNA sequencing and PCR reactions as transcription reactions do not depend upon use of a small primer nor on chain termination with dideoxynucleotides. As the method of Blakesley et al. is disclosed as a means of avoiding pyrophosphorolysis, a skilled artisan would not have applied this method to the ITT system of Swartz et al. However, upon updating the search for the instant claims, new art was uncovered and the following new grounds of rejection is deemed to apply. As such the finality of the

previous Office action is withdrawn and the following non-final Office Action is presented.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 and 15-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swartz et al. (WO 00/55353) in view of Kern et al., Pratt, and Blakesley et al. (WO 98/22615).

Swartz et al. teach *in vitro* transcription/translation systems having a variety of systems for generating the necessary ATP for nucleic acid and protein synthesis. Swartz et al. teach that such systems comprise at least ATP, an energy source, a template for production of the macromolecule, e.g. DNA, mRNA, etc., amino acids, and such co-factors, enzymes and other

reagents that are necessary for the synthesis, e.g. ribosomes, tRNA, polymerases, transcriptional factors, etc. Also included may be enzyme(s) that catalyze the regeneration of ATP from high energy phosphate bonds, e.g. acetate kinase, creatine kinase, etc. The enzymes may be present in the extracts used for translation, or may be added to the reaction mix. The cell free synthesis reaction may be performed as batch, continuous flow, or semi-continuous flow, as known in the art Swartz et al. teach that high concentrations of inorganic phosphate are inhibitory of such ITT systems (page 11).

Kern et al. teach that inorganic pyrophosphate (PP_i) is produced during transcription and is inhibitory to *in vitro* transcription reactions, at least in part due to its sequestration of Mg^{+2} in a precipitate and teach that this inhibition can be overcome by one of two possible solutions: 1) using an increased initial concentration of $Mg(OAc)_2$ or 2) using inorganic pyrophosphatase to hydrolyze the pyrophosphate to inorganic phosphate (see particularly page 755).

Pratt teach *in vitro* transcription/translation systems which comprise at least an *E. coli* S30 extract, ATP, an energy source, a template for production of the macromolecule, e.g. DNA, mRNA, etc., amino acids, and such co-factors, enzymes and other reagents that are necessary for the synthesis, e.g.

ribosomes, tRNA, polymerases, transcriptional factors, etc. Pratt teach on page 188 that high magnesium ion concentrations cause increased initiation of both transcription and translation at sites not normally used in addition to the authentic initiation sites.

Blakesley et al. teach methods for preventing inhibition of nucleic acid synthesis by inorganic pyrophosphate comprising adding ATP-sulfurylase and its substrate (adenosine 5'-phosphosulfate) to a cell-free nucleic acid synthesis system (page 11). Blakesley et al. teach that the enzyme can be isolated from natural sources or produced recombinantly (page 20) and can be added at the beginning of the reaction or supplemented in addition throughout (page 19). Blakesley et al. teach that concentration of ATP-sulfurylase may range from about 1 U/ml to about 2000 U/ml, preferably about 2 U/ml (page 19). Blakesley et al. teach that the disclosed methods be used in methods where reduction of the pyrophosphate concentration is desired and as an alternative to the inclusion of pyrophosphatase in the reactions. Blakesley et al. teach that the methods can be used with RNA polymerases (see page 15) however Blakesley et al. do not specifically teach the use of the disclosed methods with *in vitro* transcription/translation systems.

The ITT systems of Swartz et al. clearly require transcription and Kern et al. clearly teach that high levels of inorganic pyrophosphate inhibit transcription. While Kern et al. teach two possible solutions to this problem, a skilled artisan would have recognized from the disclosures of Swartz et al. and Pratt that neither of the solutions discussed by Kern et al. would have been optimum for a combined *in vitro* transcription/translation (ITT) system as Pratt disclose that increasing the magnesium ion concentration causes increased initiation of both transcription and translation at sites not normally used in addition to the authentic initiation sites and Swartz et al. teach that inorganic phosphate (i.e., the product produce by hydrolysis of the pyrophosphate with pyrophosphatase) is inhibitory to protein synthesis. As Blakesley et al. teach a third means of reducing pyrophosphate levels which is specifically disclosed as an alternative to inclusion of pyrophosphatase in nucleic acid synthesis reactions, which method does not result in increased levels of inorganic phosphate, it would have been obvious to one of ordinary skill in the art to employ the method described by Blakesley et al. to reduce the pyrophophate levels in the ITT system of Swartz et al. without either increasing the initial magnesium ion concentration or producing increased levels of inorganic

phosphate as Kern et al. teach that the pyrophosphate produced during transcription is inhibitory to transcription reactions.

In response to the previous rejection over only Swartz et al. and Blakesley et al., applicants have argued that one of ordinary skill in the art would not have found it obvious to use the method of Blakesley et al. in an *in vitro* transcription and translation system such as that of Swartz et al. as one of ordinary skill in the art would have understood that pyrophosphorolysis is not a problem in transcription reactions as it is in DNA sequencing and PCR reactions as transcription reactions do not depend upon use of a small primer nor on chain termination with dideoxynucleotides. As the method of Blakesley et al. is disclosed as a means of avoiding pyrophosphorolysis, a skilled artisan would not have applied this method to the ITT system of Swartz et al. This argument was persuasive to overcome the previous rejection. However, it is not persuasive to overcome the instant rejection over these references in combination with both Kern et al. and Pratt as Kern et al. teach that high levels of pyrophosphate are inhibitory to transcription reactions and that pyrophosphate is produced by the transcription reaction and teach that this can be overcome by the inclusion of pyrophosphatase in the reaction. The method of Blakesley et al. is clearly disclosed as a method for

reducing the pyrophosphate concentration of nucleic acid synthesis reactions in which high concentrations of pyrophosphate are detrimental and as an alternative to the inclusion of pyrophosphatase in the reactions. Furthermore the disclosures of Pratt (that high levels of magnesium ion increase the amount of aberrant transcription and translation initiation) and Swartz et al. (that high levels of inorganic phosphate inhibit protein synthesis) would clearly have motivated a skilled artisan to find another method of reducing the inorganic pyrophosphate concentration than the two solutions offered by Kern et al. The method of Blakesley et al. clearly provides just such an additional method and is further disclosed as useful with RNA polymerase. As such a skilled artisan would have found it obvious to use this method to prevent inhibition of transcription by inorganic pyrophosphate in the ITT system of Swartz et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval

(PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Prouty/
Primary Examiner
Art Unit 1652